(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

CAAGGACACC GCTGAGGGCG CCGAGCT 27

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

CGGCGCCCTC AGCGGTGTC 19

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

CAAGGACACC CCTGCAGGCG CTGAGCT 27

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CAGCGCCTGC AGGGGTGTC 19

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CAAGGACACC CCTGAGGGCG CCGCCCT 27

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

AGGGCGGCGC CCTCAGGGGT GTC 23

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

CAAGGACACC CCTGCAGGCG CCGCCCT 27

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

AGGGCGGCGC CTGCAGGGGT GTC 23

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CAAGGACGCT CCGGAGGGCG CCGCCCT 27

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

AGGGCGGCGC CCTCCGGAGC GTC 23

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

CAAGGATGCC CCGGCGGGTG CAGAGCT 27

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

CTGCACCCGC CGGGGCATC 19

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CAAGGATGCT CCGGCCGGTG CGGCCCT 27

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AGGGCCGCAC CGGCCGGAGC ATC 23

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

CAAGGACCTC AAACCATGGT ATGAGCCCAT ATAC 34

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

ATGGGCTCAT ACCATGGTTT GAGGTC 26

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Thr Pro Glu Gly Ala Glu
1 5

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Cys Gly Pro Lys Asp Thr Pro Glu Gly Ala Glu Leu Lys Pro Trp Tyr
1 5 10 15

Cys

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Cys Gly Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr
1 5 10 15

Cys

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Cys Thr Pro Glu Gly Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Glu Gly Ala Glu Leu Lys Pro Trp Tyr
1 5

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Thr Pro Glu
1

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 1..8
(D) OTHER INFORMATION: /note= "D amino acids"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Cys Thr Pro Glu Gly Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Cys Ala Pro Glu Gly Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Cys Thr Ala Glu Gly Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Cys Thr Pro Ala Gly Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Cys Thr Pro Glu Ala Ala Glu Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Binding-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Biotin-Gly-Gly is coupled to the N-terminus of the peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Cys Thr Pro Glu Gly Ala Ala Cys
1 5

CLAIMS

1. A tumor necrosis factor mutein characterized in that the TNF-α amino acid sequence is mutated, or deleted totally or partially, in the region extending from amino acid position at 101 to 116 in such a way that:
- either the lectin-like activities are modulated with respect to TNF-α,
- and/or the toxic activity is reduced with respect to TNF-α,
- and/or the inflammatory cytokines inducing capacities are modulated with respect to TNF-α,
- and/or the adhesion molecules inducing capacities are modulated with respect to TNF-α,
- and/or the metastasis promoting activity is reduced with respect to TNF-α,
- and/or the half life time is increased with respect to TNF-α, and providing that these TNF-α muteins have preferentially retained the tumoricidal activity of TNF-α, and providing that said TNF muteins are different from human TNF-α wherein amino acids 1 to 8 are replaced by a sequence within the region spanning amino acids 5 to 30 of laminin, and providing that said TNF muteins are different from human TNF-α wherein:
amino acid position 101 is Ser, hTNF-α wherein amino acid position 102 is Arg or deleted, hTNF-α wherein amino acid position 103 is Trp, hTNF-α wherein amino acid position 105 is Pro, hTNF-α wherein amino acid position 105 is Ile, hTNF-α wherein amino acid position 105 is Ile and position 44 is Cys, hTNF-α wherein amino acid position 106 is Ser, hTNF-α wherein amino acid position 106 is Ser and position 131 is Cys, hTNF-α wherein amino acid position 108 is Phe, hTNF-α wherein amino acid position 110 is Lys, hTNF-α wherein amino acid positions 111 to 112 are deleted, hTNF-α wherein amino acid position 112 is deleted or Met, hTNF-α wherein amino acid position 111 is deleted and amino acid positions 109 and 120 are respectively Gln and His, hTNF-α wherein amino acid position 115 is Ile or Cys, hTNF-α

wherein amino acid position 116 is Lys, His or Val, hTNF-α wherein amino acid positions 115-116 are Ile-Lys;
and with said TNF muteins possibly containing in their peptidic chain outside the region spanning amino acids 101 to 116 of TNF-α, additional modifications consisting of substitutions and/or deletions and/or additions of one or several amino acid residues, and with said muteins being characterized in that they have retained the aforementioned activities; or a pharmaceutically acceptable salt thereof.

2. A TNF mutein according to claim 1, further characterized in that the lectin-like activities are modulated with respect to TNF-α.

3. A TNF mutein according to any of claims 1 or 2, further characterized in that the lectin-like activities are increased with respect to TNF-α.

4. A TNF mutein according to any of claims 1 or 2, further characterized in that the lectin-like activities are reduced with respect to TNF-α.

5. A TNF mutein according to claim 1, further characterized in that the toxic activity is reduced with respect to TNF-α.

6. A TNF mutein according to claim 1, further characterized in that the inflammatory cytokine inducing capacities are modulated with respect to TNF-α.

7. A TNF mutein according to any of claims 1 or 6, further characterized in that the inflammatory cytokine inducing capacities are increased with respect to TNF-α.

8. A TNF mutein according to any of claims 1 or 6, further characterized in that the inflammatory cytokine inducing capacities are reduced with respect to TNF-α.

9. A TNF mutein according to claim 1, further characterized in that the adhesion molecule inducing capacities are modulated with respect to TNF-α.

10. A TNF mutein according to any of claims 1 or 9, further characterized in that the adhesion molecule inducing capacities are reduced with respect to TNF-α.

11. A TNF mutein according to any of claims 1 or 9, further characterized in that the adhesion molecule inducing capacities are increased with respect to TNF-α.

12. A TNF mutein according to claim 1, further characterized in that the metastasis promoting activity is reduced with respect to TNF-α.

13. A TNF mutein according to any of claims 1 to 12, further characterized in that the tumoricidal activity is retained with respect to TNF-α.

14. A TNF mutein according to any of claims 1 to 12, further characterized in that the tumoricidal activity is reduced with respect to TNF-α.

15. A TNF mutein according to any of claims 1 to 14, further characterized in it shows an increased half life time with respect to TNF-α.

16. A TNF mutein according to any of claims 1 to 15, characterized in that at least part of the region extending from amino acid positions 101 to 116 of TNF-α, or the complete region corresponding to amino acid positions 101 to 116 of TNF-α has been deleted, and preferably at least the region covering amino acid positions 105 to 110 has been deleted.

17. A TNF mutein according to any of claims 1 to 15, characterized in that at least one of the amino acids in the region extending from amino acids 101 to 116 of TNF-α, and preferably at least one of the amino acids in the region extending from amino acids 105 to 110, has been mutated or deleted.

18. A Nucleic acid sequence encoding any of the polypeptides according to claims 1 to 17.

19. A process for the preparation of the polypeptides according to any of claims 1 to 17, comprising the steps of:

- transformation of an appropriate cellular host with a vector, particularly a plasmid, a cosmid, a phage or a virus, in which a nucleic acid sequence according to claim 18 coding for at least one of the polypeptides according to any of claims 1 to 17 has been inserted (insert) under the control of the appropriate regulatory elements, particularly a promoter recognized by the polymerases of the cellular host and, in the case of a procaryotic host, an appropriate ribosome binding site (RBS), enabling the expression in said cellular host of said nucleic acid sequence,
- culture of said transformed cellular host under conditions enabling the expression of said insert.

20. A TNF mutein according to any of claims 1 to 17, for treating illnesses and pathological conditions such as, sepsis, septic shock, Gram negative sepsis, endo-toxic shock, toxic shock syndrome, cachexia, microbial infections, rheumatoid arthritis, inflammatory conditions, respiratory distress syndrome, pulmonary fibrosis, infections, graft-versus-host-disease, reperfusion damage such as myocardial ischaemia, AIDS, cancer, cerebral malaria, immunosuppression, etc.

21. A pharmaceutical composition, containing as active substance, at least anyone of the TNF mutein polypeptides according to any

of claims 1 to 17, in association with a pharmaceutical acceptable vehicle.

22. Use of a TNF mutein characterized in that the TNF-α amino acid sequence is mutated, or deleted totally or partially, in the region extending from amino acid position at 101 to 116 in such a way that:
- either the lectin-like activities are modulated with respect to TNF-α,
- and/or the toxic activity is reduced with respect to TNF-α,
- and/or the inflammatory cytokines inducing capacities are modulated with respect to TNf-α,
- and/or the adhesion molecules inducing capacities are modulated with respect to TNF-α,
- and/or the metastasis promoting activity is reduced with respect to TNF-α,
- and/or show an increased half life time with respect to TNF-α,
and providing that these TNF-α muteins have preferentially retained the tumoricidal activity of TNF-α,
and with said TNF muteins possibly containing in their peptidic chain outside amino acid region 101 to 116 of TNF-α, additional modifications consisting of substitutions and/or deletions and/or additions of one or several amino acid residues, and with said muteins being characterized in that they have retained the aforementioned activities; or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating illnesses and pathological conditions, such as, sepsis, septic shock, Gram negative sepsis, endo-toxic shock, toxic shock syndrome, cachexia, microbial infections, rheumatoid arthritis, inflammatory conditions, respiratory distress syndrome, pulmonary fibrosis, infections, graft-versus-host-disease, reperfusion damage such as myocardial ischaemia, AIDS, cancer, cerebral malaria, immunosuppression, etc.

23. Use of an antibody specifically detecting an epitope residing in the region comprising amino acids 101 to 116 of TNF-α, more

particularly a monoclonal antibody, characterized in that it:
- either modulates the lectin-like activities of TNF-α,
- and/or inhibits the toxic activity of TNF-α,
- and/or modulates the inflammatory cytokines inducing capacities of TNf-α,
- and/or modulates the adhesion molecules inducing capacities of TNF-α,
- and/or inhibits the metastasis promoting activity of TNF-α,
for the preparation of a medicament for treating TNF-induced septic shock or illnesses or pathological conditions associated with the in vivo activities of TNF-α.

24. Use of an immunological complex comprising a monoclonal antibody according to claim 23, and complete TNF-α, for the preparation of a medicament for treating illnesses such as tumors.

25. Use of an antisense peptide of a peptide comprising at least part of the region 101 to 116 of TNF-α, more particularly a monoclonal antibody, characterized in that it :
- either modulates the lectin-like activities of TNF-α,
- and/or inhibits the toxic activity of TNF-α,
- and/or modulates the inflammatory cytokines inducing capacities of TNf-α,
- and/or modulates the adhesion molecules inducing capacities of TNF-α,
- and/or inhibits the metastasis promoting activity of TNF-α,
foı the preparation of a medicament for treating TNF-induced septic shock or illnesses or pathological conditions associated with the lectin-like effects of TNF-α.

26. Use of a complex comprising an antisense peptides according to claim 25 and TNF-α for the preparation of a medicament for treating illnesses such as tumors.

27. Use of an antibody or antisense peptide according to any of

claims 23 to 26, characterized in that said antibody or said peptide modulates the lectin-like activities of TNF-α.

28. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide inhibits the lectin-like activities of TNF-α.

29. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide stimulates the lectin-like activities of TNF-α.

30. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide inhibits the toxic activity of TNF-α.

31. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide modulates the inflammatory cytokines inducing capacities of TNF-α.

32. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide inhibits the inflammatory cytokines inducing capacities of TNF-α.

33. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide modulates the adhesion molecules inducing capacities of TNF-α.

34. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide inhibits the adhesion molecules inducing capacities of TNF-α.

35. Use of an antibody or antisense peptide according to any of

claims 23 to 26, characterized in that said antibody or said peptide stimulates the adhesion molecules inducing capacities of TNF-α.

36. Use of an antibody or antisense peptide according to any of claims 23 to 26, characterized in that said antibody or said peptide inhibits the metastasis promoting activity TNF-α.

37. Use of an antibody or antisense peptide according to any of claims 24 or 26, characterized in that said antibody or said peptide increases the half life time of TNF-α.

38. Cells transfected with a nucleic acid according to claim 18 coding for the TNF muteins according to any of claims 1 to 17, said nucleic acid being inserted into any suitable vector, with said cells being preferably autologous cells derived from the patient (e.g. a cancer patient) to be treated with such compositions; and with said vector-insert combination being constructed in such a way as to allow continuous expression of the TNF mutein at either a constant level, or at a level which can be modified, depending on the exact nature of the vector used to make the vector-insert combination.

39. Pharmaceutical composition containing as active substance transfected cells according to claim 38, in association with a pharmaceutical acceptable vehicle.

40. Use of transfected cells according to claim 38, for the preparation of a medicament for treating illnesses such as cancer.

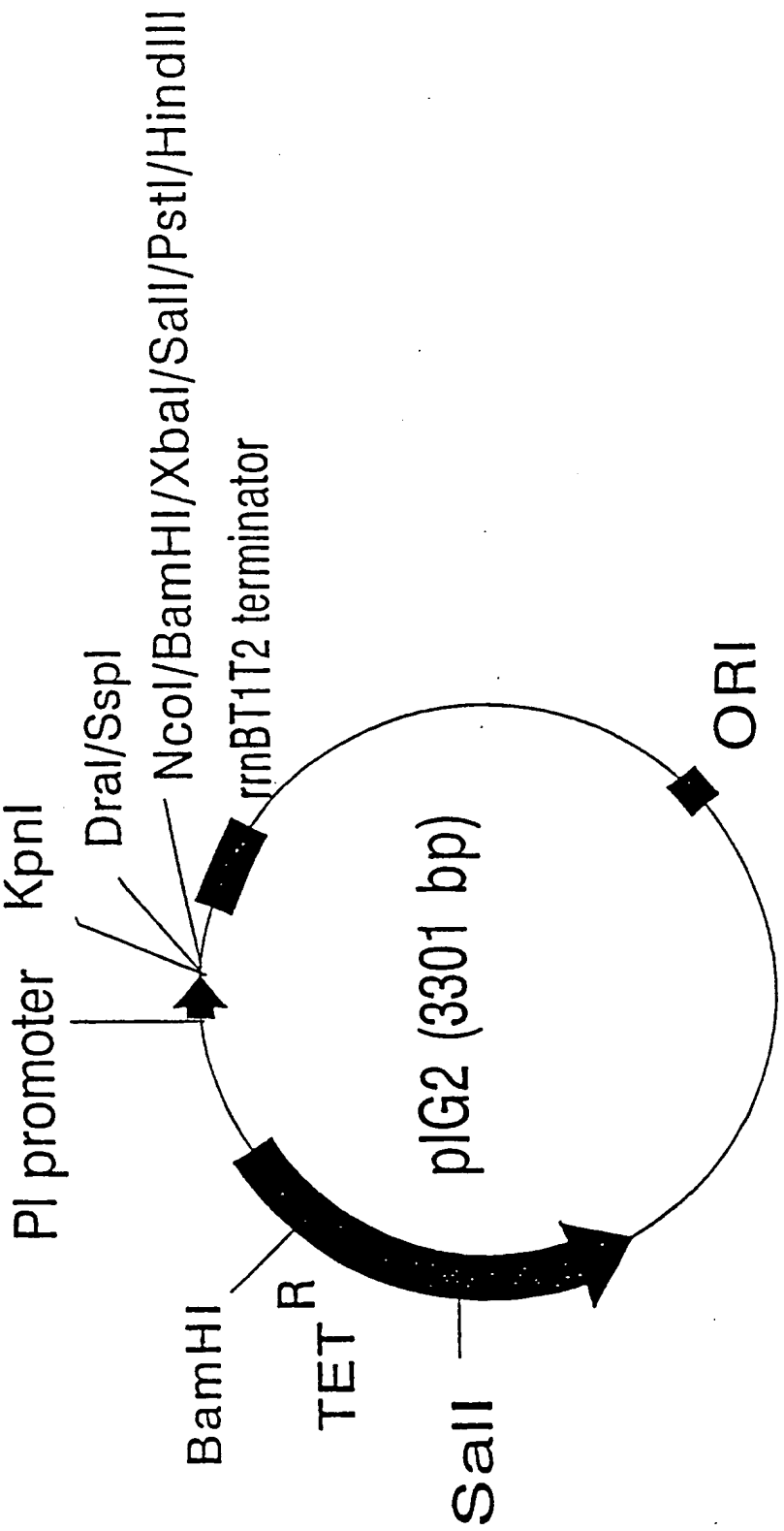
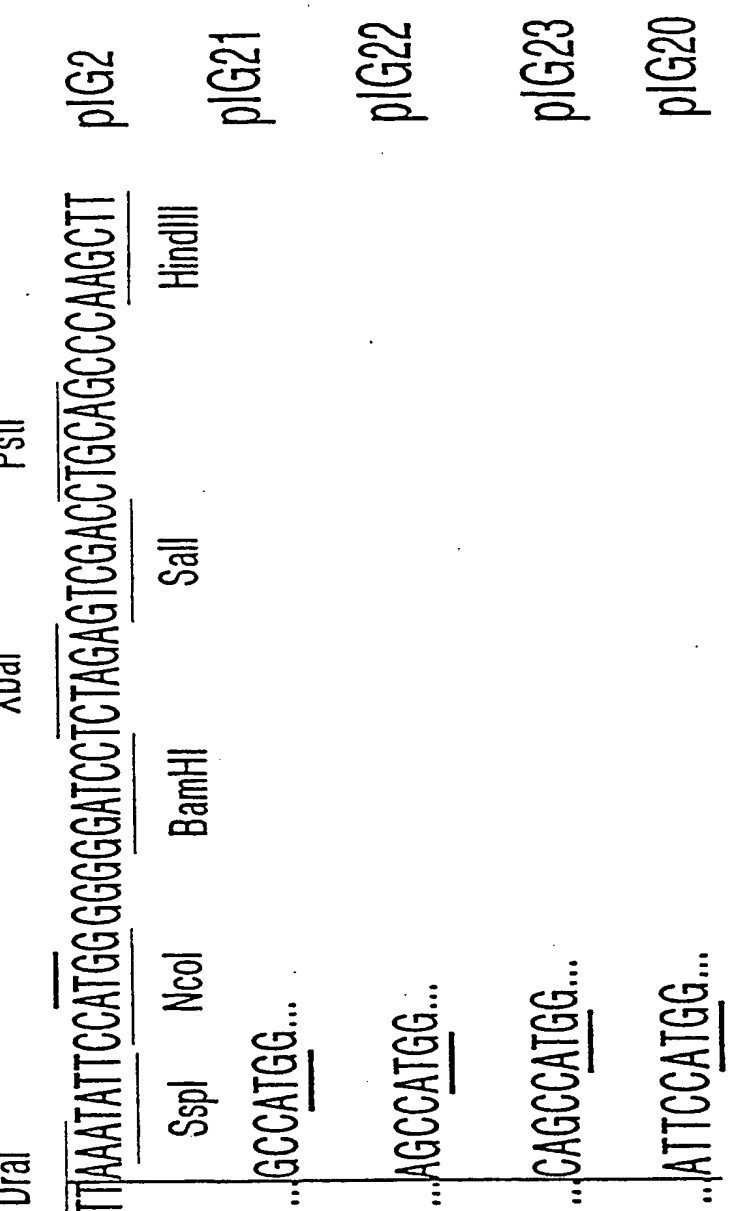

PI promoter
KpnI
DraI/SspI
NcoI/BamHI/XbaI/SalI/PstI/HindIII
rrnBT1T2 terminator
ORI
pIG2 (3301 bp)
BamHI
TET R
SalI

Figure 1A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DraI
XbaI
PstI
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NcoI
BamHI
SalI
HindIII
...GCCATGG...
...AGCCATGG...
...CAGCCATGG...
...ATTCCATGG...
pIG2
pIG21
pIG22
pIG23
pIG20

Figure 1B

```
TTCCGGGGAT CTCTCACCTA CCAAACAATG CCCCCCTGCA AAAAATAAAT TCATATAAAA   60
AACATACAGA TAACCATCTG CGGTGATAAA TTATCTCTGG CGGTGTTGAC ATAAATACCA  120
CTGGCGGTGA TACTGAGCAC ATCAGCAGGA CGCACTGACC ACCATGAAGG TGACGCTCTT  180
AAAAATTAAG CCCTGAAGAA GGGCAGGGGT ACCAGGAGGT TTAAATATTC CATGGGGGGG  240
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CAGCCTGATA CAGATTAAAT CAGAACGCAG AAGCGGTCTG ATAAAACAGA ATTTGCCTGG  360
CGGCAGTAGC GCGGTGGTCC CACCTGACCC CATGCCGAAC TCAGAAGTGA AACGCCGTAG  420
CGCCGATGGT AGTGTGGGGT CTCCCCATGC GAGAGTAGGG AACTGCCAGG CATCAAATAA  480
AACGAAAGGC TCAGTCGAAA GACTGGGCCT TTCGTTTTAT CTGTTGTTTG TCGGTGAACG  540
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TCAAATATGT ATCCGCTCAT GAGACAATAA CCCTGATAAA TGCTTCAATA ATAAAAGGAT  780
CTAGGTGAAG ATCCTTTTTG ATAATCTCAT GACCAAAATC CCTTAACGTG AGTTTTCGTT  840
CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT  900
GCGCGTAATC TGCTGCTTGC AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC  960
```

Figure 2

```
GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG CGCAGATACC 1020
AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT CTGTAGCACC 1080
GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT GCTGCCAGTG GCGATAAGTC 1140
GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT AAGGCGCAGC GGTCGGGCTG 1200
AACGGGGGGT TCGTGCACAC AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA 1260
CCTACAGCGT GAGCATTGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG CGGACAGGTA 1320
TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG GAGCTTCCAG GGGGAAACGC 1380
CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA CTTGAGCGTC GATTTTTGTG 1440
ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC AACGCGGCCT TTTTACGGTT 1500
CCTGGCCTTT TGCTGGCCTT TTGCTCACAT GTTCTTTCCT GCGTTATCCC CTGATTCTGT 1560
GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT CGCCGCAGCC GAACGACCGA 1620
GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCTGA CTTCCGCGTT TCCAGACTTT 1680
ACGAAACACG GAAACCGAAG ACCATTCATG TTGTTGCTCA GGTCGCAGAC GTTTTGCAGC 1740
AGCAGTCGCT TCACGTTCGC TCGCGTATCG GTGATTCATT CTGCTAACCA GTAAGGCAAC 1800
CCCGCCAGCC TAGCCGGGTC CTCAACGACA GGAGCACGAT CATGCGCACC CGTGGCCAGG 1860
ACCCAACGCT GCCCGAGATG CGCCGCGTGC GGCTGCTGGA GATGGCGGAC GCGATGGATA 1920
```

Figure 2 - Continuation 1

TGTTCTGCCA AGGGTTGGTT TGCGCATTCA CAGTTCTCCG CAAGAATTGA TTGGCTCCAA 1980

TTCTTGGAGT GGTGAATCCG TTAGCGAGGT GCCGCCGGCT TCCATTCAGG TCGAGGTGGC 2040

CCGGCTCCAT GCACCGCGAC GCAACGCGGG GAGGCAGACA AGGTATAGGG CGGCGCCTAC 2100

AATCCATGCC AACCCGTTCC ATGTGCTCGC CGAGGCGGCA TAAATCGCCG TGACGATCAG 2160

CGGTCCAGTG ATCGAAGTTA GGCTGGTAAG AGCCGCGAGC GATCCTTGAA GCTGTCCCTG 2220

ATGGTCGTCA TCTACCTGCC TGGACAGCAT GGCCTGCAAC GCGGGCATCC CGATGCCGCC 2280

GGAAGCGAGA AGAATCATAA TGGGGAAGGC CATCCAGCCT CGCGTCGCGA ACGCCAGCAA 2340

GACGTAGCCC AGCGCGTCGG CCGCCATGCC GGCGATAATG GCCTGCTTCT CGCCGAAACG 2400

TTTGGTGGCG GGACCAGTGA CGAAGGCTTG AGCGAGGGCG TGCAAGATTC CGAATACCGC 2460

AAGCGACAGG CCGATCATCG TCGCGCTCCA GCGAAAGCGG TCCTCGCCGA AAATGACCCA 2520

GAGCGCTGCC GGCACCTGTC CTACGAGTTG CATGATAAAG AAGACAGTCA TAAGTGCGGC 2580

GACGATAGTC ATGCCCCGCG CCCACCGGAA GGAGCTGACT GGGTTGAAGG CTCTCAAGGG 2640

CATCGGTCGA CGCTCTCCCT TATGCGACTC CTGCATTAGG AAGCAGCCCA GTAGTAGGTT 2700

GAGGCCGTTG AGCACCGCCG CCGCAAGGAA TGGTGCATGC AAGGAGATGG CGCCCAACAG 2760

TCCCCCGGCC ACGGGGCCTG CCACCATACC CACGCCGAAA CAAGCGCTCA TGAGCCCGAA 2820

GTGGCGAGCC CGATCTTCCC CATCGGTGAT GTCGGCGATA TAGGCGCCAG CAACCGCACC 2880

Figure 2 - Continuation 2

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TGTGGCGCCG GTGATGCCGG CCACGATGCG TCCGGCGTAG AGGATCCACA GGACGGGTGT  2940

GGTCGCCATG ATCGCGTAGT CGATAGTGGC TCCAAGTAGC GAAGCGAGCA GGACTGGGCG  3000

GCGGCCAAAG CGGTCGGACA GTGCTCCGAG AACGGGTGCG CATAGAAATT GCATCAACGC  3060

ATATAGCGCT AGCAGCACGC CATAGTGACT GGCGATGCTG TCGGAATGGA CGATATCCCG  3120

CAAGAGGCCC GGCAGTACCG GCATAACCAA GCCTATGCCT ACAGCATCCA GGGTGACGGT  3180

GCCGAGGATG ACGATGAGCG CATTGTTAGA TTTCATACAC GGTGCCTGAC TGCGTTAGCA  3240

ATTTAACTGT GATAAACTAC CGCATTAAAG CTTATCGATG ATAAGCTGTC AAACATGAGA  3300

GCCCCGCGCC CACCGGAAGG AGCTGACTGG GTTGAAGGCT CTCAAGGGCA TCGGTCGACG  3360

CTCTCCCTTA TGCGACTCCT GCATTAGGAA GCAGCCCAGT AGTAGGTTGA GGCCGTTGAG  3420

CACCGCCGCC GCAAGGAATG GTGCATGCAA GGAGATGGCG CCCAACAGTC CCCCGGCCAC  3480

GGGGCCTGCC ACCATACCCA CGCCGAAACA AGCGCTCATG AGCCCGAAGT GGCGAGCCCG  3540

ATCTTCCCCA TCGGTGATGT CGGCGATATA GGCGCCAGCA ACCGCACCTG TGGCGCCGGT  3600

GATGCCGGCC ACGATGCGTC CGGCGTAGAG GATCCACAGG ACGGGTGTGG TCGCCATGAT  3660

CGCGTAGTCG ATAGTGGCTC CAAGTAGCGA AGCGAGCAGG ACTGGGCGGC GGCCAAGCG  3720

GTCGGACAGT GCTCCGAGAA CGGGTGCGCA TAGAAATTGC ATCAACGCAT ATAGCGCTAG  3780

CAGCACGCCA TAGTGACTGG CGATGCTGTC GGAATGGACG ATATCCCGCA AGAGGCCCGG  3840

CAGTACCGGC ATAACCAAGC CTATGCCTAC AGCATCCAGG GTGACGGTGC CGAGGATGAC  3900

GATGAGCGCA TTGTTAGATT TCATACACGG TGCCTGACTG CGTTAGCAAT TTAACTGTGA  3960

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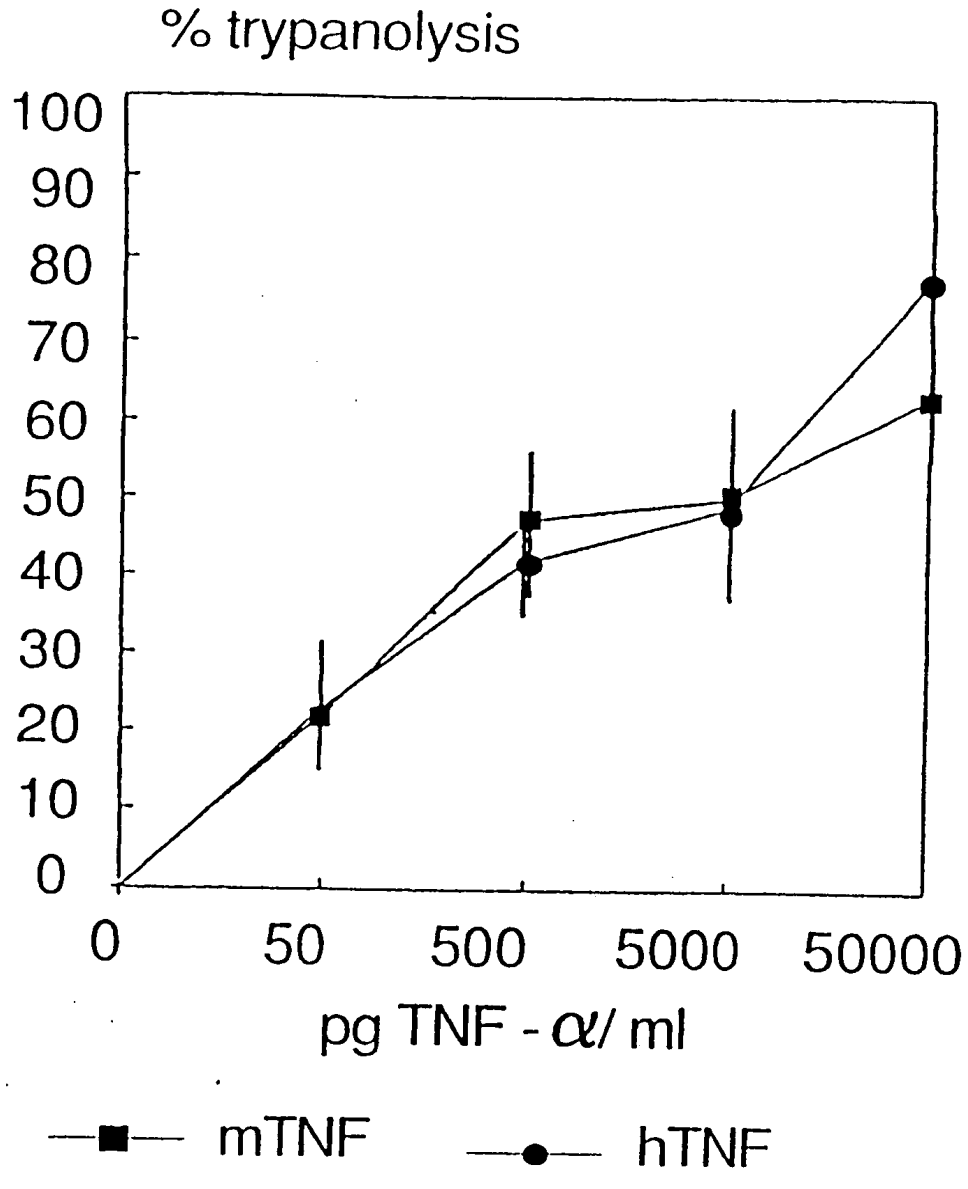

Figure 3A

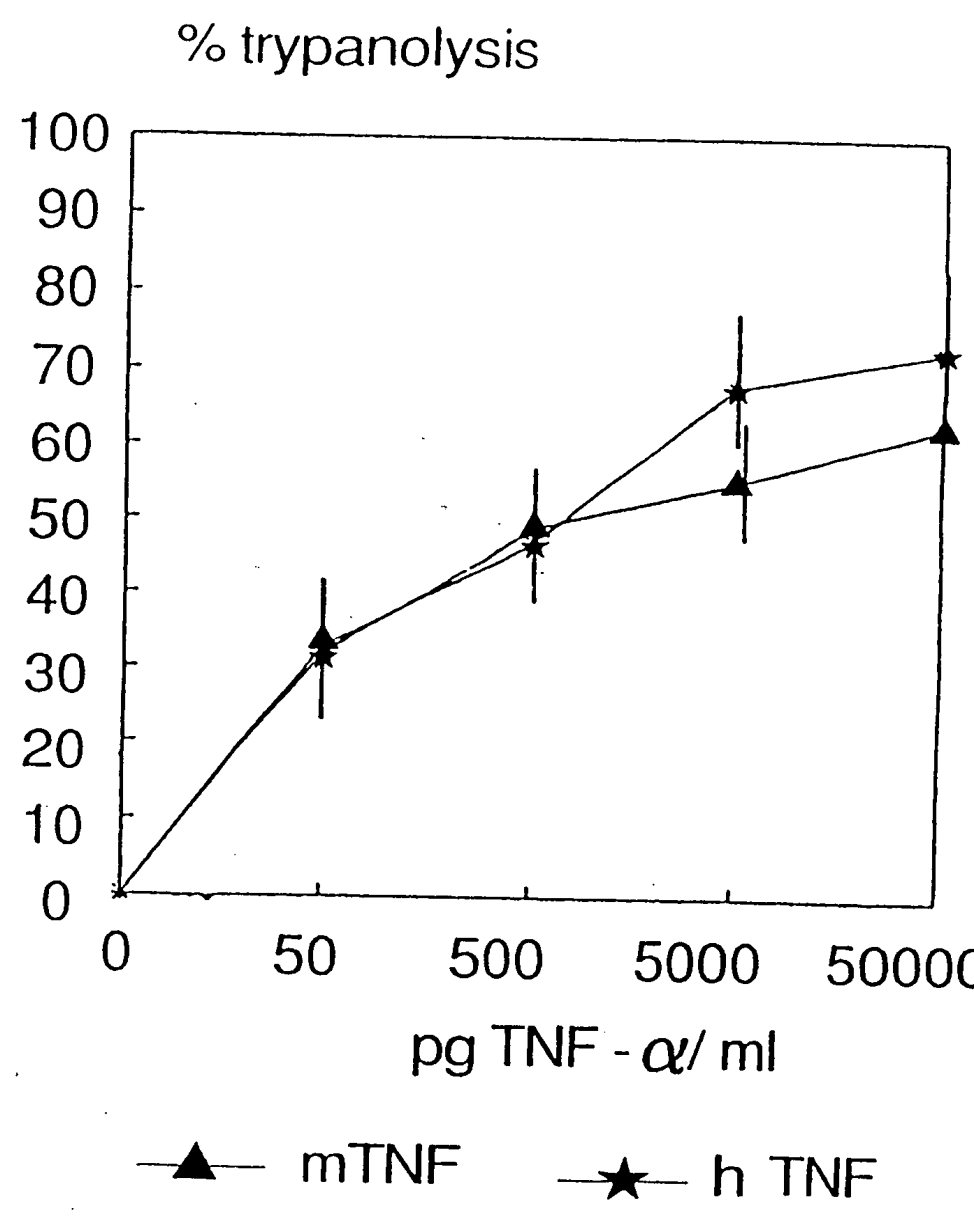

Figure 3B

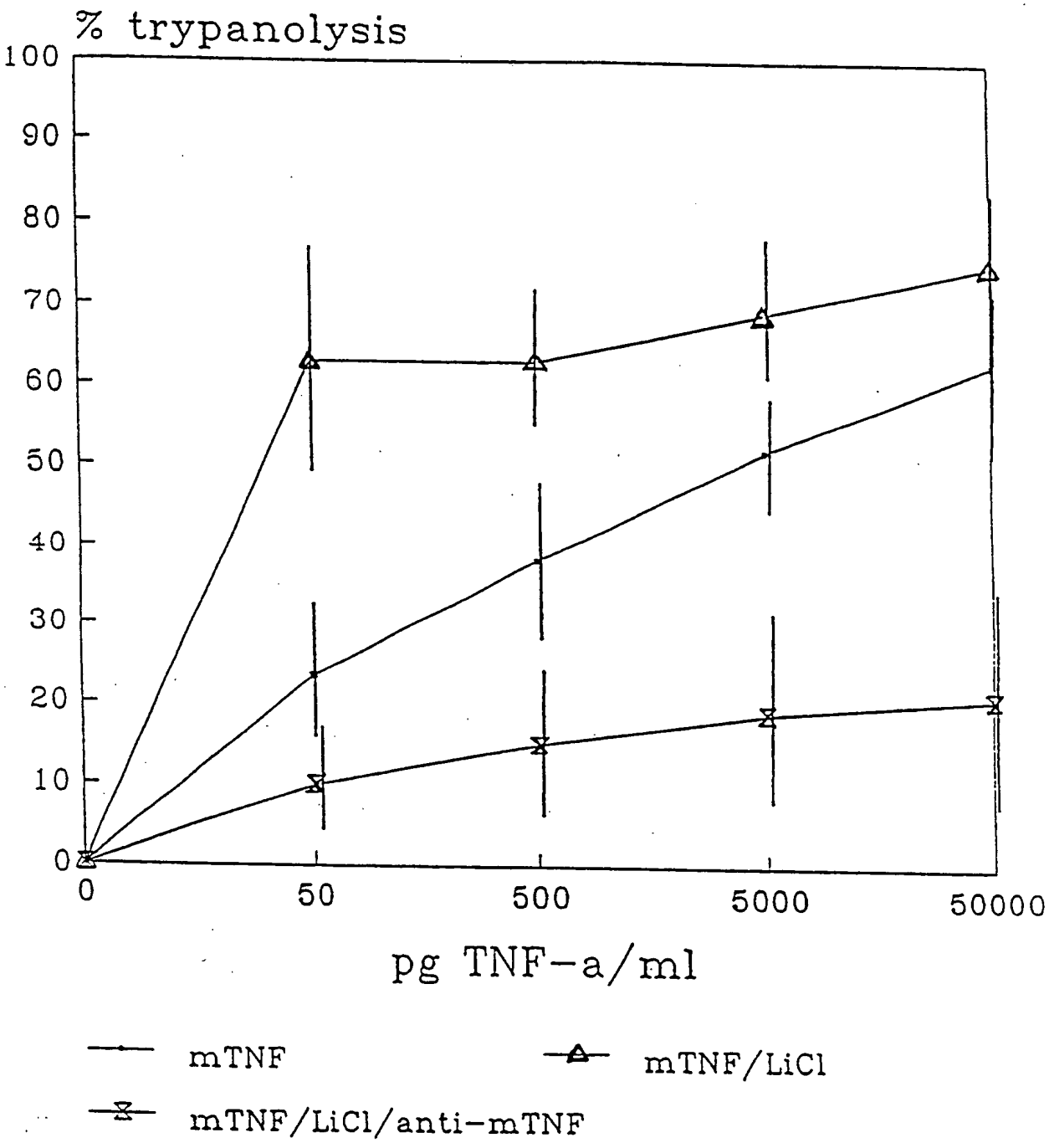
% trypanolysis
100
90
80
70
60
50
40
30
20
10
0
0
50
500
5000
50000
pg TNF-a/ml
mTNF
mTNF/LiCl
mTNF/LiCl/anti-mTNF

Figure 4

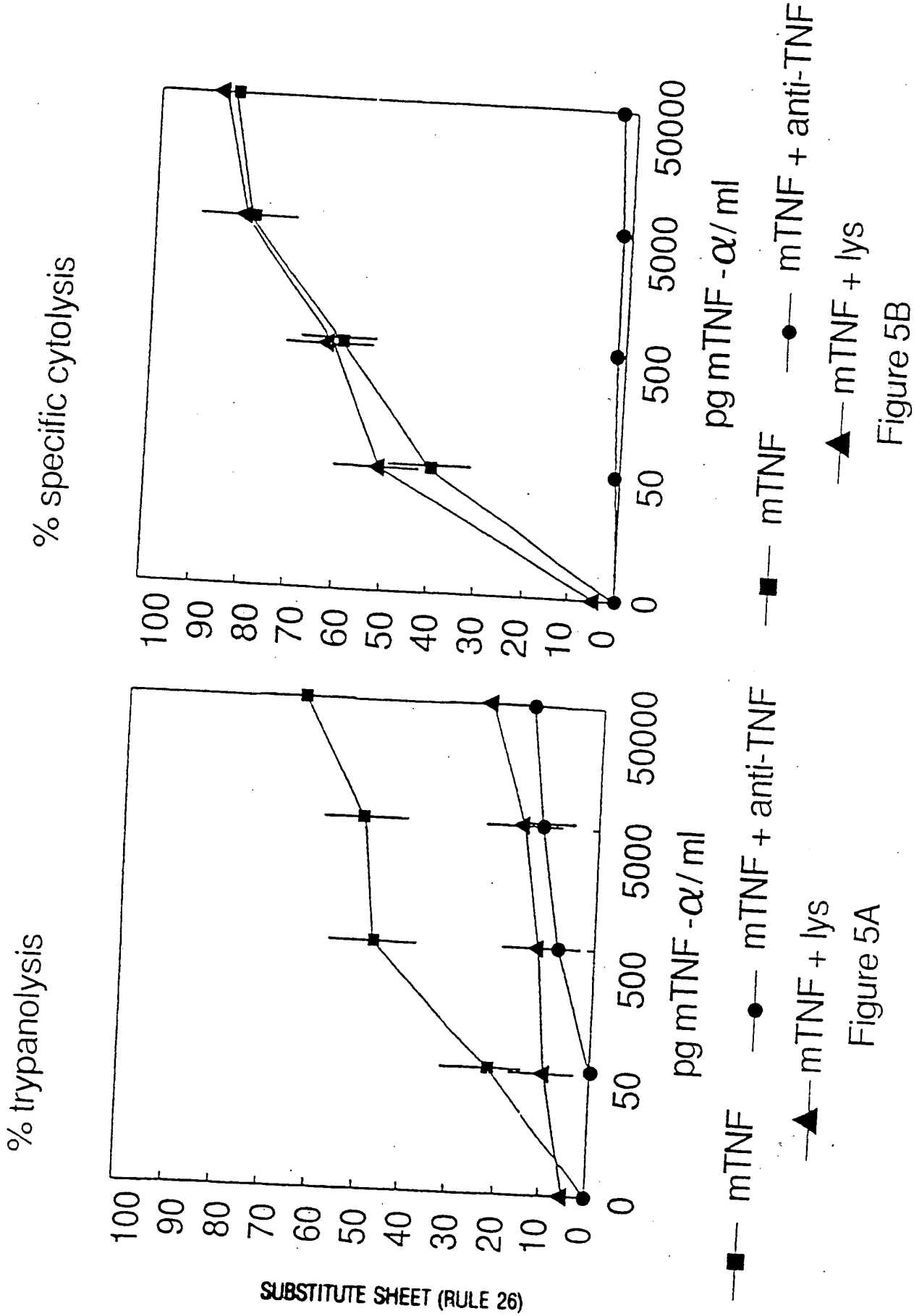

Figure 5A

Figure 5B

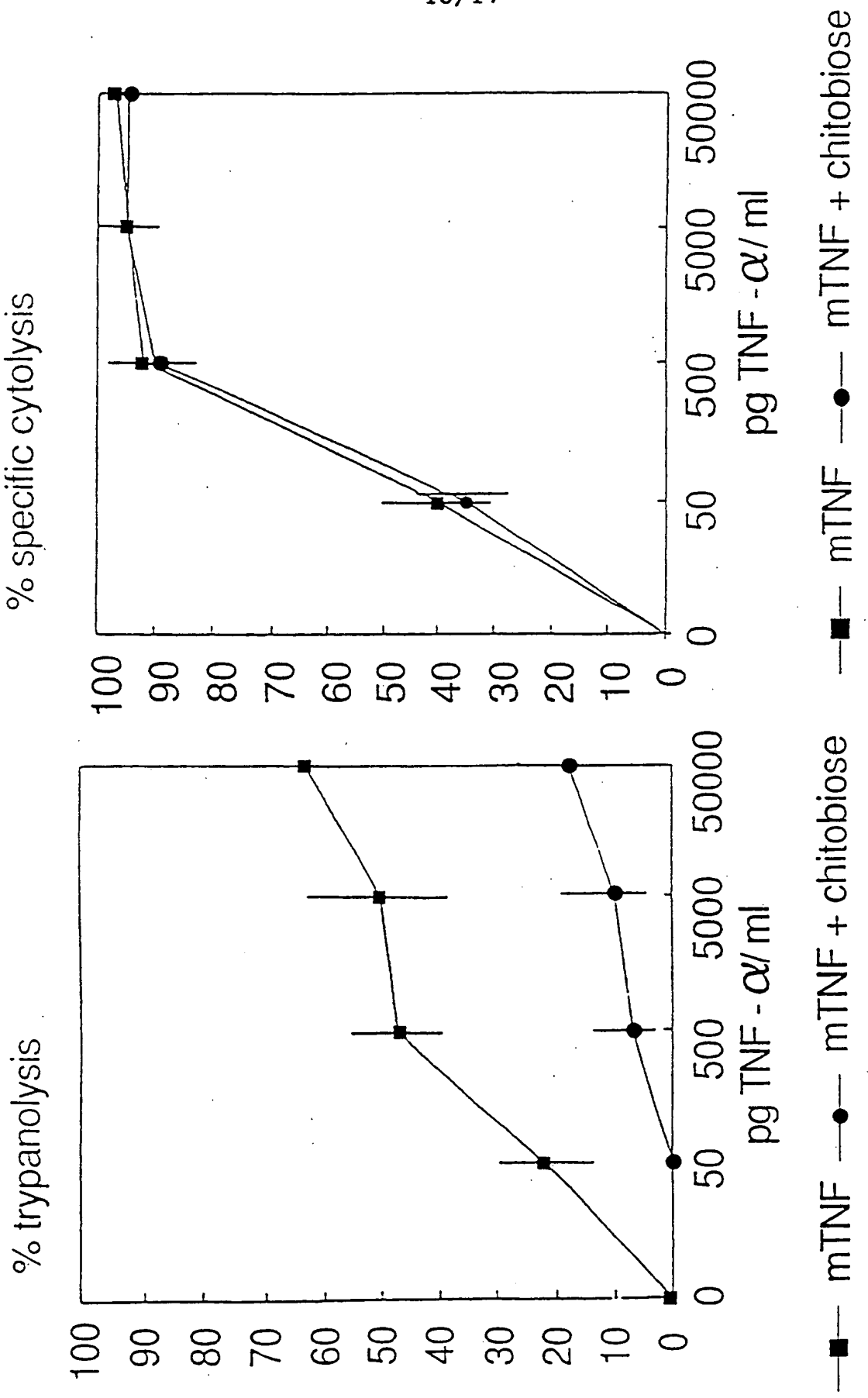

Figure 6B

Figure 6A

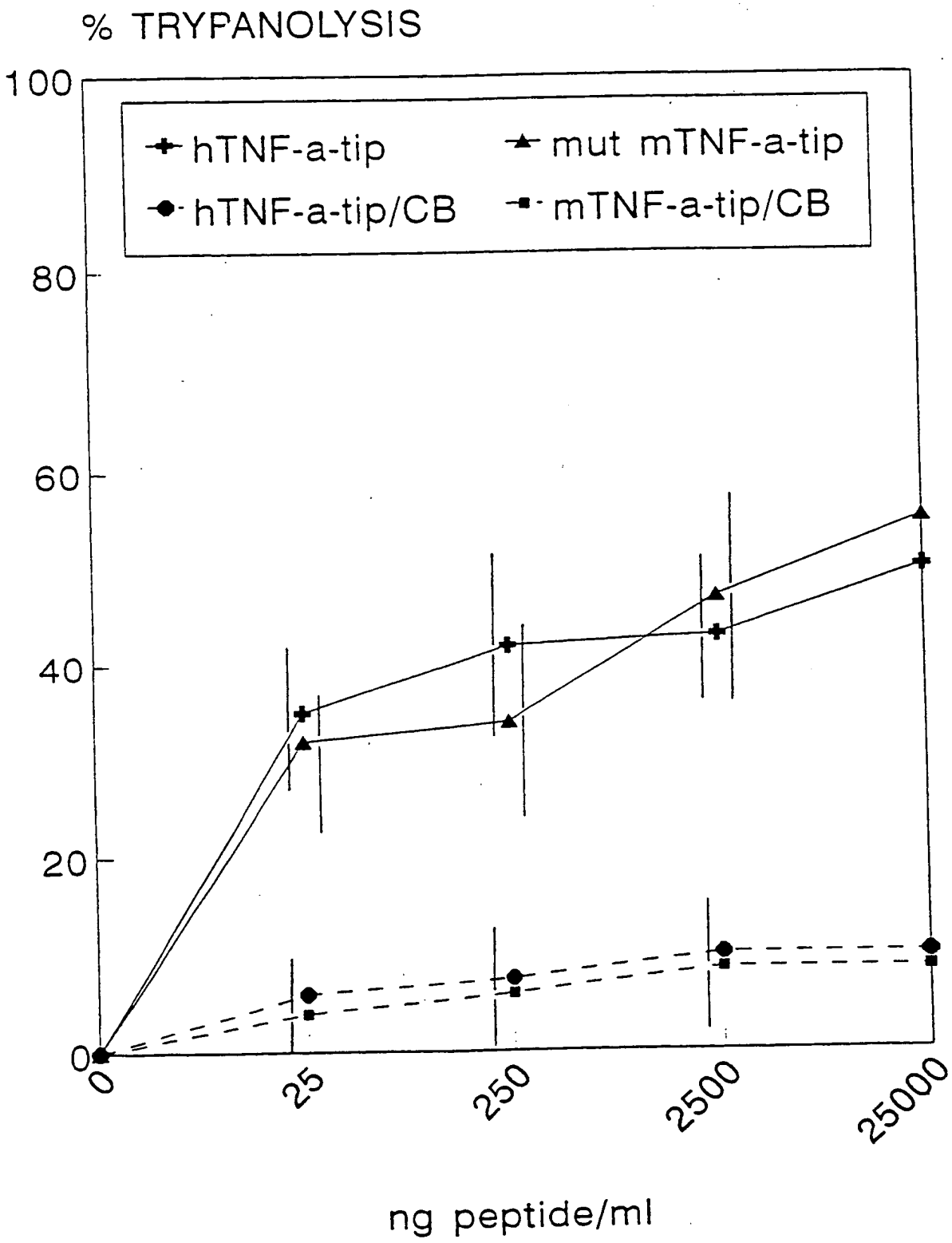
% TRYPANOLYSIS
100
80
60
40
20
0
hTNF-a-tip
mut mTNF-a-tip
hTNF-a-tip/CB
mTNF-a-tip/CB
0
25
250
2500
25000
ng peptide/ml

Figure 7

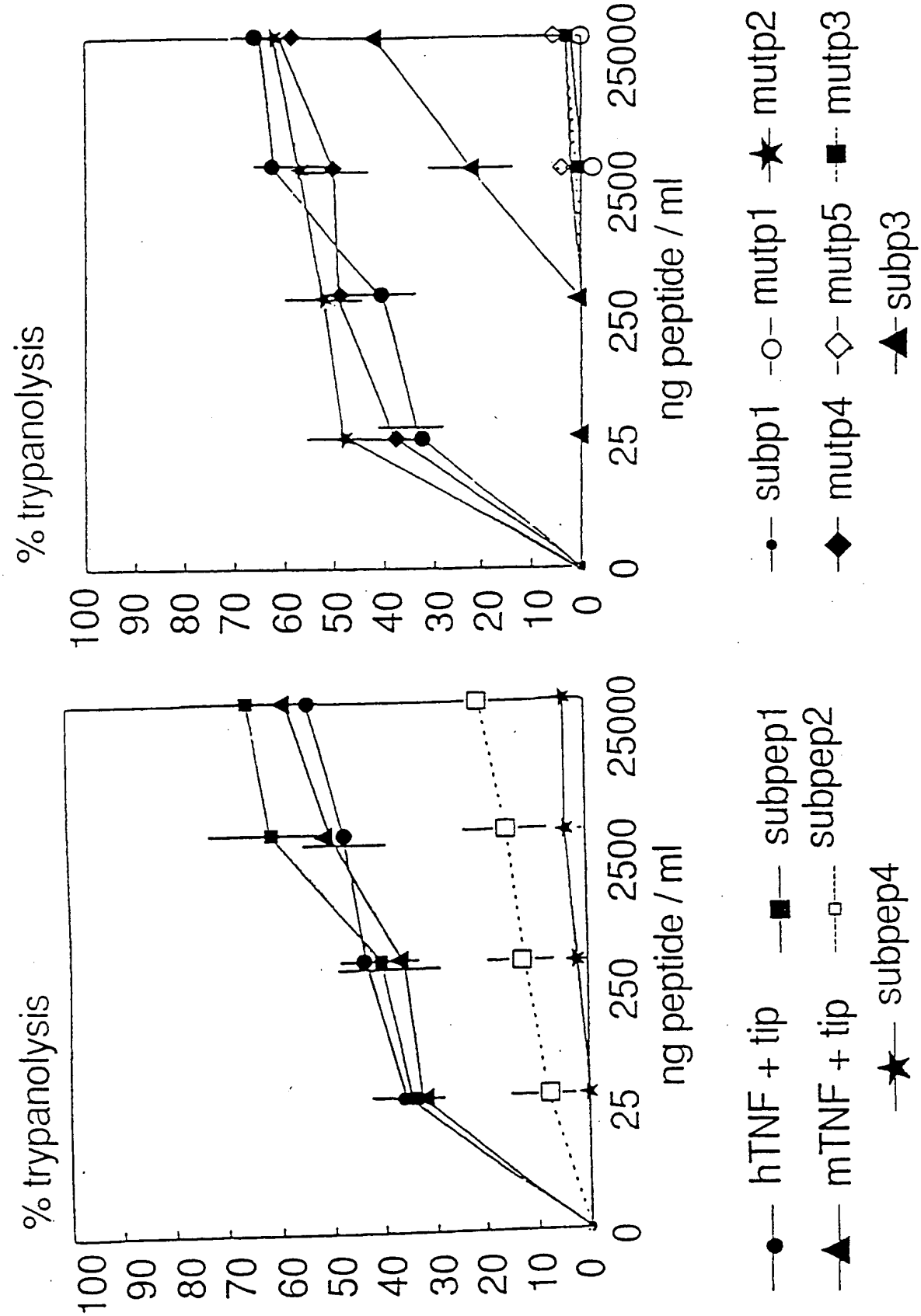

Figure 8

Figure 9

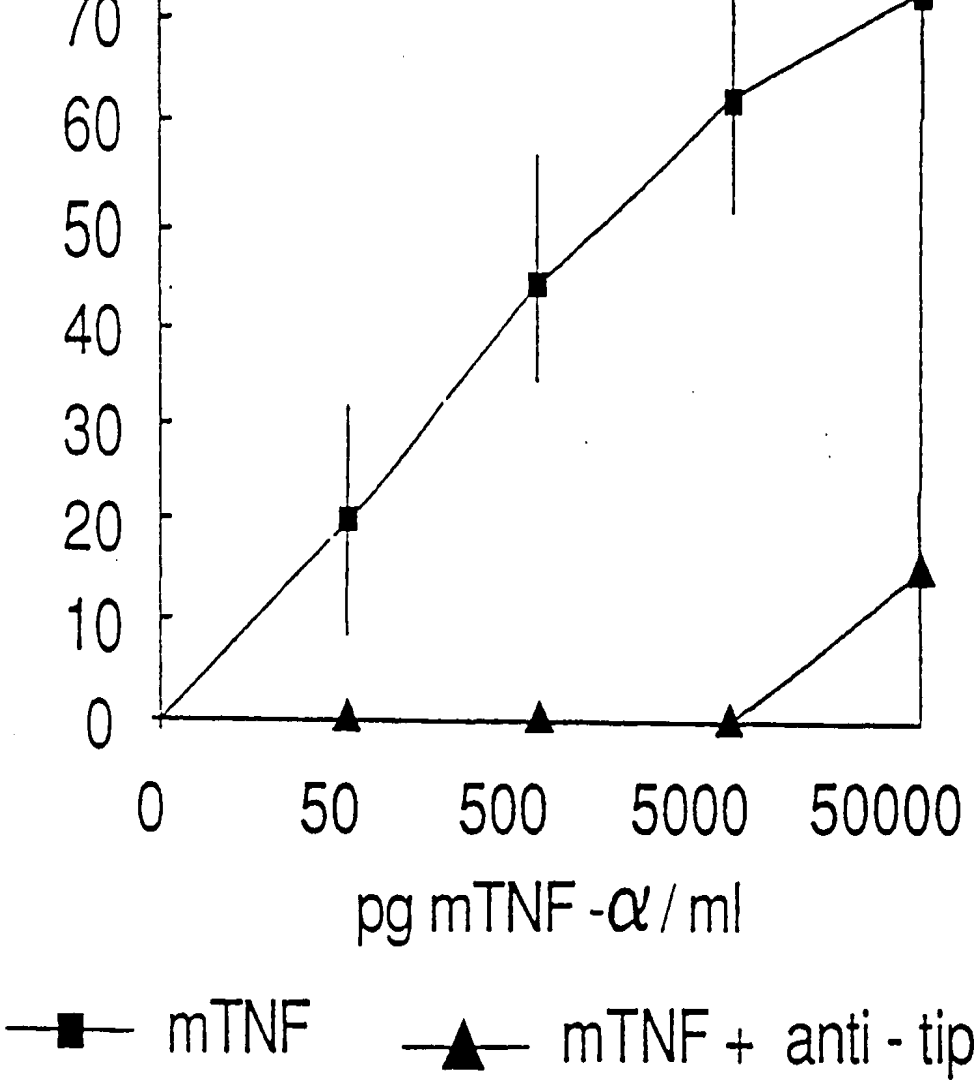
70
60
50
40
30
20
10
0
0
50
500
5000
50000
pg mTNF -α / ml
mTNF
mTNF + anti - tip

Figure 10

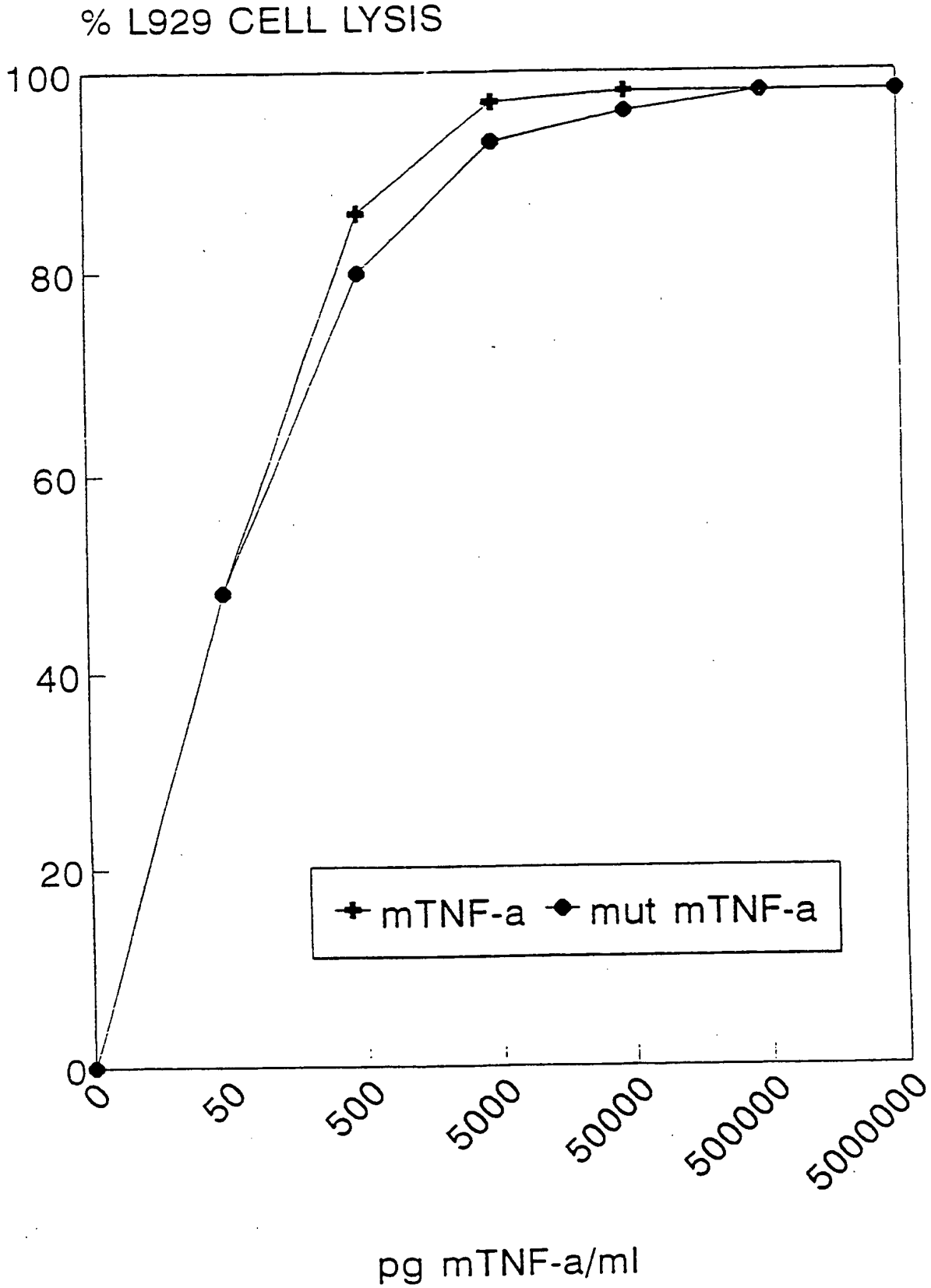
% L929 CELL LYSIS
100
80
60
40
20
0
0
50
500
5000
50000
500000
5000000
mTNF-a
mut mTNF-a
pg mTNF-a/ml

Figure 11

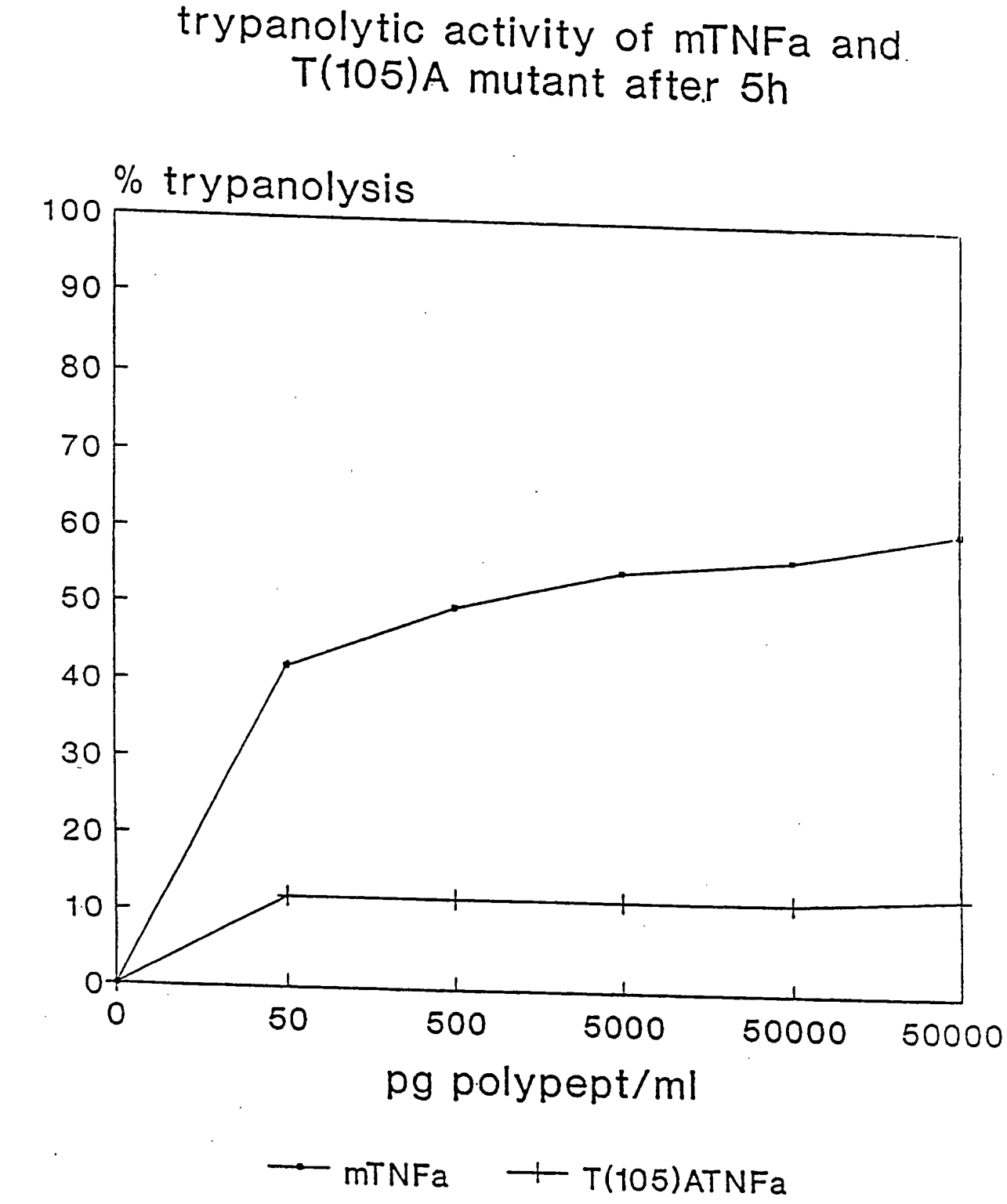
trypanolytic activity of mTNFa and T(105)A mutant after 5h
% trypanolysis
100
90
80
70
60
50
40
30
20
10
0
0
50
500
5000
50000
50000
pg polypept/ml
mTNFa
T(105)ATNFa
medium : PSG + 1% NMS

Figure 12

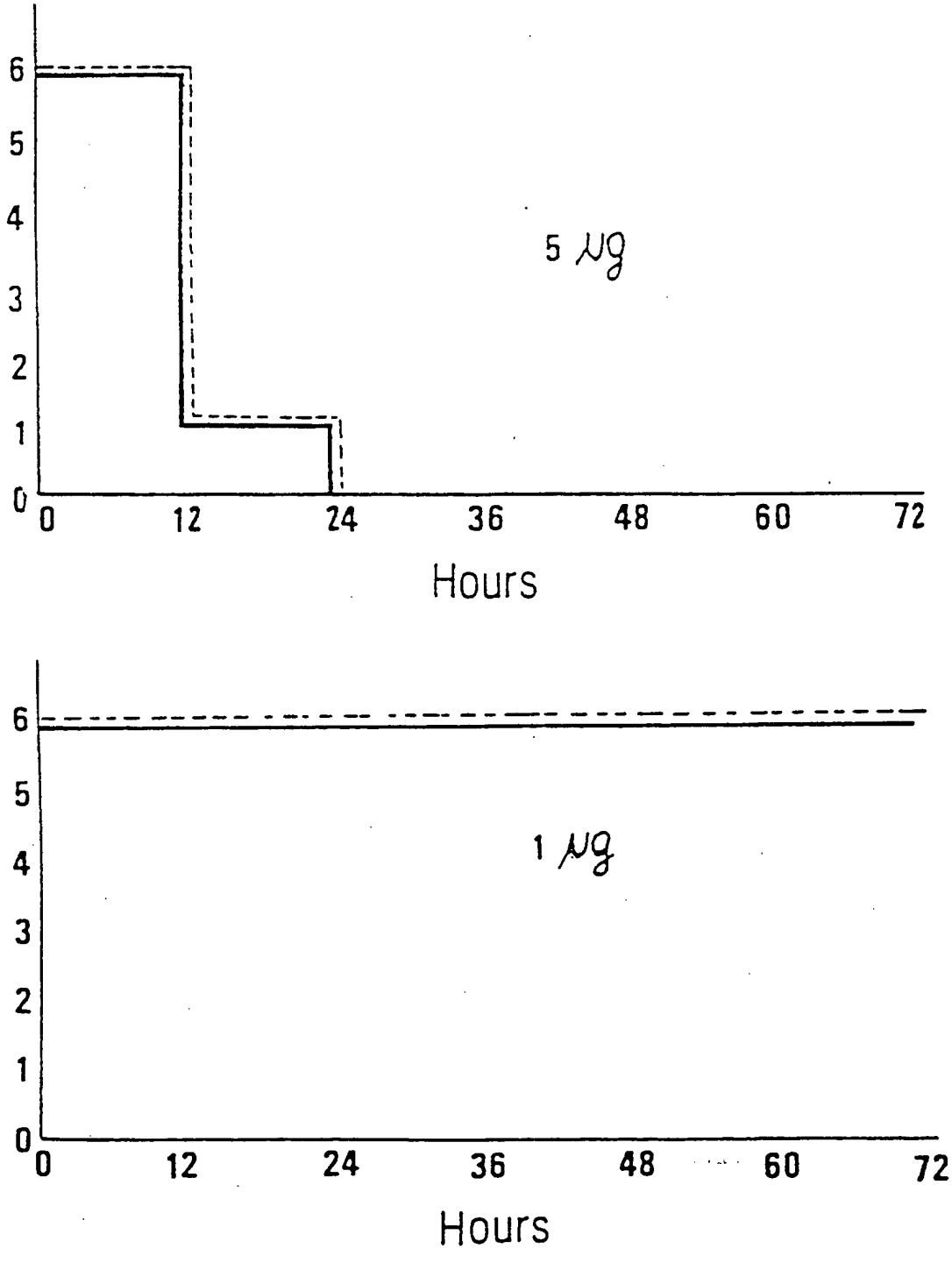
6
5
4
3
2
1
0
5 µg
0
12
24
36
48
60
72
Hours
6
5
4
3
2
1
0
1 µg
0
12
24
36
48
60
72
Hours

Figure 13

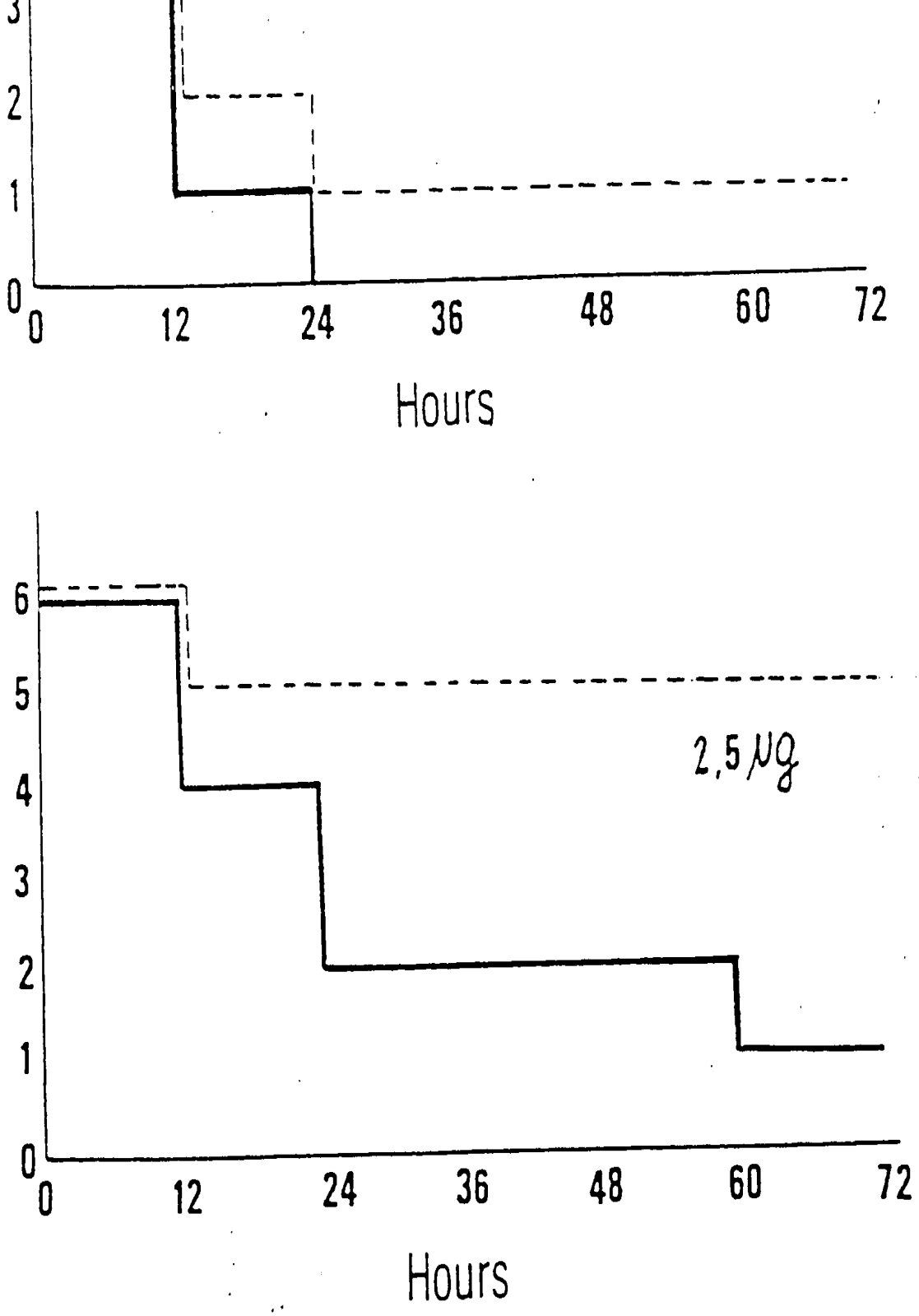

Figure 13 - continuation

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C12N15/28 C07K15/00 A61K37/02 A61K39/395 C12N5/10
C12P21/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROTEIN ENGINEERING vol. 3 , 1990 pages 713 - 719 J. YAMAGISHI ET AL.; 'Mutational analysis of structure-activity relationships in human tumor necrosis factor-alpha' *abstract; Table II(a) and (b); discussion* ---	1,18-24, 38-40
X	PROTEIN ENGINEERING vol. 3 , 1990 pages 721 - 724 T. ARAKAWA ET AL.; 'Alteration in folding efficiency and conformation of recombinant human tumor necrosis factor-alpha by replacing cysteines 69 and 101 with aspartic acid 69 and arginine 101' *abstract* --- -/--	1,18-24, 38-40

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 June 1994	01. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Yeats, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 168 214 (GENENTECH, INC.) 15 January 1986 *page 15, line 32 - page 18, line 27; pages 63-66; claims*	1,18-24, 38-40
X	EP,A,0 479 071 (ISHIHARA SANGYO KAISHA, LTD.) 8 April 1992 *claims 1-19*	1,18-24, 38-40
A	EP,A,0 414 607 (ROUSSEL-UCLAF) 27 February 1991 *claims*	25
T	SCIENCE vol. 263 , 11 February 1994 pages 814 - 817 R. LUCAS ET AL.; 'Mapping the lectin-like activity of tumor necrosis factor' *whole document*	1-40

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0168214	15-01-86	US-A-	4650674	17-03-87
		AU-B-	599571	26-07-90
		AU-A-	4465285	09-01-86
		JP-A-	61040221	26-02-86
		KR-B-	9310767	10-11-93
EP-A-0479071	08-04-92	JP-A-	4368397	21-12-92
		US-A-	5247070	21-09-93
EP-A-0414607	27-02-91	FR-A-	2651130	01-03-91
		AU-B-	642423	21-10-93
		AU-A-	6119090	28-02-91
		CA-A-	2023899	24-02-91
		CN-A-	1049668	06-03-91
		FR-A-	2667202	27-03-92
		JP-A-	3091485	17-04-91